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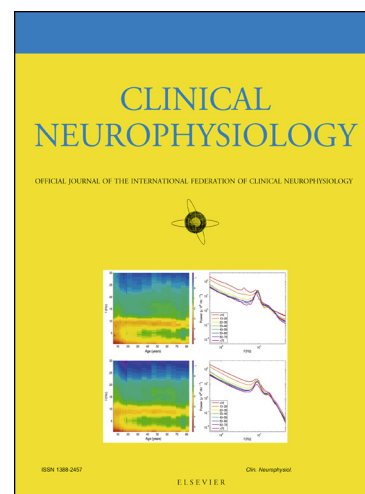
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**The effect of transcranial direct current stimulation on motor sequence learning and
upper limb function after stroke**

Melanie K Fleming^{a*}, John C Rothwell^b, Laszlo Sztriha^c, James T Teo^{b,c}, Di J Newham^a

^aCentre of Human and Aerospace Physiological Sciences, King's College London, UK

^bInstitute of Neurology, University College London, UK

^cDept of Stroke & Neurology, Princess Royal University Hospital, King's College Hospital NHS
Foundation Trust, UK

*** Corresponding author:**

Melanie Fleming

Centre of Human and Aerospace Physiological Sciences

Faculty of Life Sciences and Medicine

King's College London

3.11 Shepherd's House, Guy's Campus, London SE1 1UL, UK

Tel.: +44 207 848 6679

Fax: +44 207 848 6325

E-mail: melanie.fleming@kcl.ac.uk

Highlights

- Stroke survivors demonstrated sequence specific learning, irrespective of transcranial direct current stimulation (tDCS) condition.
- Improvement in the Jebsen Taylor Test was seen after unilateral motor cortex tDCS but not after bihemispheric motor cortex tDCS.
- Changes in performance with tDCS were independent of changes in transcallosal inhibition.

Abstract

Objective: To assess the impact of electrode arrangement on the efficacy of tDCS in stroke survivors and determine whether changes in transcallosal inhibition (TCI) underlie improvements.

Methods: 24 stroke survivors (3-124 months post-stroke) with upper limb impairment participated. They received blinded tDCS during a motor sequence learning task, requiring the paretic arm to direct a cursor to illuminating targets on a monitor. Four tDCS conditions were studied (crossover); anodal to ipsilesional M1, cathodal to contralesional M1, bihemispheric, sham. The Jebsen Taylor hand function test (JTT) was assessed pre- and post-stimulation and TCI assessed as the ipsilateral silent period (iSP) duration using transcranial magnetic stimulation.

Results: The time to react to target illumination reduced with learning of the movement sequence, irrespective of tDCS condition ($p>0.1$). JTT performance improved after unilateral tDCS (anodal or cathodal) compared with sham ($p<0.05$), but not after bihemispheric ($p>0.1$). There was no effect of tDCS on change in iSP duration ($p>0.1$).

Conclusions: Unilateral tDCS is effective for improving JTT performance, but not motor sequence learning.

Significance: This has implications for the design of future clinical trials.

Keywords: Stroke, Upper limb function, Transcranial direct current stimulation, Motor sequence learning; Transcallosal inhibition.

1. Introduction

Stroke is a leading cause of adult disability and many people are left with impairments and are dependent on others for activities of daily living (Dobkin, 2005, DOH, 2007, Veerbeek et al. , 2011). Strategies to improve plasticity and enhance motor learning are needed. One potential approach is to use transcranial direct current stimulation (tDCS) to enhance the effect of physical therapy.

After unilateral stroke it has been proposed that there is an interhemispheric imbalance in transcallosal inhibition between the two motor cortices with excess inhibition of the ipsilesional primary motor cortex (M1) by the “undamaged” contralesional M1 (Murae et al. , 2004, Nowak et al. , 2009, Takeuchi et al. , 2010, Takeuchi et al. , 2012, Wessel et al. , 2015). The result is that the ipsilesional M1 is “doubly disabled” both by the lesion and by the excess inhibition from the contralesional hemisphere. To tackle this imbalance three main strategies for delivering tDCS have been proposed; i) anodal to increase excitability of the ipsilesional M1, ii) cathodal to decrease excitability of the contralesional M1 or iii) both anodal and cathodal applied simultaneously (bihemispheric). Bihemispheric stimulation could hypothetically provide additional benefit over unilateral by targeting both cortices concurrently. However, the impact of electrode arrangement on motor learning and function after stroke is unclear and requires systematic investigation.

Physical therapy can be regarded as a form of motor learning in which the damaged motor system is re-trained to optimise the function of its remaining output. Experimentally, motor learning is commonly assessed as changes in motor preparation, speed and accuracy with

the repetition of a movement sequence or pattern. However, there are very few paradigms which enable assessment of motor sequence learning using the paretic arm in stroke survivors with upper limb impairment. We developed such a paradigm, requiring gross movements of the arm to direct a cursor to targets on a monitor which illuminated in a repeating order. Here we used this paradigm to systematically assess the impact of tDCS electrode arrangement on within session motor sequence learning and upper limb function in stroke survivors with mild and moderate impairment. We used the Jebsen Taylor hand function test (JTT) (Jebsen et al. , 1969) as a marker of upper limb function as this timed test is valid and responsive (Jebsen et al. , 1969, Beebe et al. , 2009) and has been used previously to detect changes within an experimental session (Fregni et al. , 2005, Hummel et al. , 2005, Mahmoudi et al. , 2011). We also aimed to determine whether changes in learning or JTT performance with tDCS would depend on changes in transcallosal inhibition (TCI). We hypothesised that within-session improvements in learning and JTT performance would be evident with active tDCS in comparison with sham. Based on the interhemispheric imbalance model we predicted that bihemispheric tDCS would provide additional enhancement over unilateral stimulation and that improvements would be associated with an increase in TCI from the ipsilesional to the contralesional M1.

2. Methods

2.1 Participants

Potential participants were identified between March 2014 and May 2016 from three National Health Service (NHS) trusts, stroke user groups and word of mouth. Eighty stroke survivors underwent an initial screening and agreed to be followed up. Of these, 25

participants were eligible and consented to take part (Figure 1). Participant characteristics are presented in Table 1. Time since stroke and stroke location were determined from medical records.

Inclusion criteria were; aged >18 years, first monohemispheric stroke >3 months duration, unilateral upper limb impairment and physically able to complete the motor sequence learning task with the affected hand. Exclusion criteria were; contraindications to transcranial magnetic stimulation (TMS) such as epilepsy or seizures, cardiac pacemakers or metal implants in the head. All participants provided written informed consent and the study was approved by the National Research Ethics Service and adopted by the UK National Institute for Health Research (NIHR) clinical research portfolio (UKCRN ID: 16299).

2.2 Study design

This was a single-blinded crossover study. Participants attended five sessions in total with the time of day kept as consistent as possible and each session lasting ~1.5 hours. The first session was for familiarisation with the protocols. The remaining four were experimental sessions; tDCS was delivered during the motor sequence learning task, and the JTT and TCI were assessed pre- and post-stimulation.

2.2.1 Familiarisation session

Participants practiced the motor sequence learning task and the JTT in order to minimise potential differences between sessions due to familiarisation with the protocols.

Familiarisation of the JTT involved 10 repetitions of each task, or until performance time stabilised (mean (SD): 7 (2) repetitions). For the motor sequence learning task, participants

completed as many repetitions as necessary to ensure they felt comfortable with the use of the computer mouse with the affected hand and understood the purpose of the task (mean (SD): 11 (6) repetitions).

2.2.2 *Experimental sessions*

The four experimental sessions were conducted using a within-subject crossover design with sessions at least one week apart (mean (SD): 11 (7) days). The crossover design was chosen in an attempt to control for inter-individual variation in upper limb function and ability to learn the movement sequence. In each session, participants initially performed three repetitions of the JTT, followed by TMS (to localise M1 and assess TCI). The tDCS was then delivered for the first 20 minutes of the motor sequence learning task (which took on average 24 minutes to complete). TCI was then re-assessed and an additional three repetitions of the JTT performed. One participant was unable to tolerate long durations of TMS and so it was used to localise M1 but TCI was not assessed. Two other participants did not undergo TMS (one found it painful, one had a seizure >30 years earlier) and M1 was localised using C3/C4 of the 10-20 EEG system. Similarly, this method was used to locate the ipsilesional M1 if it was not possible to elicit a motor evoked potential (MEP).

2.3 **Motor sequence learning task**

This was performed using a custom designed Matlab programme (The Mathworks Inc., Massachusetts, USA), as described previously (Fleming et al. , 2016). Participants sat at a table with a computer mouse on it, in front of a computer monitor (17 inch square) showing four grey circular targets (2.3 cm diameter) and a red central square (10.9 cm²; Fig. 2). The targets were equidistant from the central square. They used their paretic hand to hold the

computer mouse which had been modified by removing the buttons. When the cursor was directed into the central square a target would illuminate (changing from grey to white) 0.3 s later, indicating that the mouse should be moved to direct the cursor into the illuminated target. To ensure accuracy of movement, a dwell time in the target was imposed where the cursor had to remain there for 0.4 s before it would return to grey. They then returned the cursor to the central square for illumination of the next target. This was an “explicit” learning task; participants were informed that they would repeat a sequence of 12 movements, 25 times, and that they should anticipate target appearance if they knew which would illuminate next.

In each experimental session, participants initially completed two practice sequences to re-familiarise them with the movements required. They were then reminded of the purpose of the task. The sequence for each participant and session was chosen randomly from a pool of eight sequences. Following completion of the 25 repetitions, two random sequences (12 movements) were performed to distinguish between general learning and sequence specific learning effects.

Values for onset time (OT), movement time (MT) and path length (PL) were automatically computed by the programme. OT was recorded as the time, in seconds, between the target illuminating and the cursor leaving the central square. Values for each repetition were normalised to the first repetition (herein referred to as “normalised OT”) and values < 1 indicate improved OT. MT was the time, in seconds, from the cursor leaving the central square to arriving in the illuminated target. PL was the number of pixels the cursor travelled to get from the central square to the target, indicating the accuracy of the movement.

Speed of cursor movement was calculated manually by dividing PL by MT. To quantify changes in the speed-accuracy trade-off a performance index (PI) was calculated (Lefebvre et al. , 2012a, Lefebvre et al. , 2012b). Initially, constant values were calculated for accuracy (a) and speed (b) using pilot data without stimulation (not shown). The PL error was calculated for each repetition of the sequence (during stimulation) as the difference between the median PL for each repetition and the minimum PL required to reach the targets. The PL error index was calculated for each repetition as the accuracy constant (a) divided by the PL error (i.e. $a / \text{PL error}$). Increases in the PL error index therefore indicate improvements in movement accuracy. The speed index was calculated by dividing the median speed for each repetition by the speed constant (speed / b). Increases in the speed index therefore indicate improvements in movement speed. The PI was calculated by multiplying the PL error index by the velocity index (i.e. $(a / \text{PL error}) \times (\text{speed} / b)$). The value for each repetition was expressed relative to the first repetition of the sequence. Values > 1 indicate improvement in either speed or accuracy without a reciprocal decrement in the other, or improvements in both speed and accuracy.

Values for OT and PI were averaged across consecutive repetitions to form 13 blocks for analysis. Learning was quantified as the change in normalised OT and PI over the blocks and the specificity of learning as the difference between the last block of the repeated sequence and the random block.

2.4 Stimulation of primary motor cortex

2.4.1 Setup

TMS was used in each session to determine the position of the M1 representation of each first dorsal interosseus (FDI) muscle for placement of the tDCS electrodes and to assess TCI pre- and post-stimulation.

Electromyography (EMG) was recorded from each FDI using pairs of 13mm Ag/AgCl Biotab electrodes (Unomedical Ltd, UK), following standard skin preparation techniques. Ground electrodes were placed over the ulnar styloid (23 mm Ag/AgCl Biotab electrode). The analogue signal was pre-amplified 1000× (Digitimer Ltd, Hertfordshire, UK) and bandpass filtered at 30-1000 Hz (Neurolog filter module, Digitimer Ltd, UK) with a 50 Hz notch filter. Data were acquired at 2 kHz, A to D converted (1401, Cambridge Electronic Design Ltd (CED), UK), recorded (Signal 4.07, CED, UK) and stored for off-line analysis as required. Motor evoked potentials (MEPs) were elicited using a figure-of-eight coil (70 mm diameter) with a Magstim 200 or Magstim 200² Bistim stimulator (Magstim Company, UK), while participants rested their hands on a pillow on their laps. The optimal position for evoking MEPs in the relaxed FDI was marked with a water-soluble marker directly on the scalp to ensure consistent coil placement during each session.

The resting motor threshold (RMT) was determined in the first experimental session. This was done in a standard manner, as the minimum intensity eliciting an MEP of $\geq 50 \mu\text{V}$ in the relaxed FDI from at least 4 out of 8 consecutive stimuli.

2.4.2 Transcallosal inhibition

TCI was assessed as the ipsilateral silent period (iSP) duration from each FDI, using a TMS intensity of 80 % maximum stimulator output (MSO), similar to previous studies (Chen et al.

, 2003, Trompetto et al. , 2004, Stinear et al. , 2008, Spagnolo et al. , 2013, Stinear et al. , 2015). Participants were instructed to produce an isometric contraction of the FDI muscle of one hand at approximately 75 % of their maximal effort, while 20 single pulse stimuli were delivered to the ipsilateral M1. Both hemispheres were tested and the hand/hemisphere to be tested first was chosen randomly. The iSP duration was calculated using Signal 4.07 (CED, UK). Each trace was rectified and an average waveform constructed. The pre-stimulus root mean square (RMS) EMG was calculated for a 450 ms period ending 10 ms before the stimulus. The iSP duration (ms) was calculated from the time where the rectified EMG activity dropped below 75 % of the pre-stimulus level to when it returned above 75 %. This level of activity was chosen for onset and offset of the iSP to ensure a method of analysis that would be objective and robust. An average duration was calculated for each FDI pre- and post-tDCS in each session and the change in iSP duration calculated. If the participant could not sustain a voluntary contraction of the paretic hand then iSP duration was assessed for the “unaffected” FDI only (representing ipsilesional to contralesional M1 TCI).

2.4.3 Transcranial direct current stimulation

For the experimental sessions tDCS was delivered for the first 20 minutes of the motor sequence learning task at 1 mA using a constant current stimulator (Neuroconn, Rogue Resolutions, UK) with two carbon electrodes encased in 25 cm² saline-soaked sponges (current density 0.04 mA.cm⁻²). For anodal tDCS the anode was placed over ipsilesional M1 (FDI “hotspot”) and the cathode over the contralateral supraorbital ridge, for cathodal tDCS the cathode was placed over contralesional M1 and the anode over the contralateral supraorbital ridge, and for bihemispheric tDCS the anode was placed over ipsilesional M1 and the cathode over contralesional M1. Sham tDCS was delivered in a standard manner, in

either of the electrode arrangements (randomly chosen). The order of tDCS conditions was randomised using a Latin square design and participants were blinded by placing sponges on all four scalp locations (bilateral M1, bilateral supraorbital ridge), although only two contained electrodes.

2.5 Jebsen Taylor test performance

Three repetitions of the JTT were completed at the beginning and end of each experimental session and the average time (s) determined. The percentage change in time for post-stimulation compared with pre-stimulation was calculated (% Δ JTT). Additionally, the % Δ JTT for the “fine motor” and “gross motor” subsections of the JTT were calculated separately.

2.6 Statistical Analysis

Based on a previous motor sequence learning study (Zimerman et al. , 2012), it was estimated that for an effect size of 0.67 at least 20 participants would be required to find a difference in learning (OT difference between last block of repeated sequence and random sequence) between active and sham stimulation with $\alpha=0.05$ and power of 80%.

Analysis was conducted using SPSS 21.0 (IBM Inc.). Normality was assessed using Kolmogorov-Smirnov tests and visual inspection of frequency histograms, and non-parametric tests were utilised if the assumption of normality was not sustained and transformation was ineffective. Adjustments were made for violations of sphericity using the Greenhouse-Geisser correction. Data are presented as mean \pm standard error of the mean (SEM) and significance was set at $p < 0.05$, unless otherwise specified.

2.6.1 *Motor sequence learning task*

To determine whether learning occurred, and whether this depended on the tDCS condition, a two way-repeated measures analysis of variance (rmANOVA) was conducted using normalised OT and PI, with factors of block (blocks 2–13) and tDCS (sham, anodal, cathodal, bihemispheric). To assess the specificity of learning, a two-way rmANOVA was conducted with factors of block (last repeated, random) and tDCS (sham, anodal, cathodal, bihemispheric). To determine whether tDCS improved sequence specific learning, a one-way rmANOVA with factors of tDCS (sham, anodal, cathodal, bihemispheric) was conducted using the values for the difference in OT between the last block of the repeated sequence and the random block.

2.6.2 *Jebsen Taylor test performance*

A one-way rmANOVA with factors of tDCS (sham, anodal, cathodal, bihemispheric) was used to determine whether there was an effect of tDCS condition on the % Δ JTT. To assess whether any differences in response between active electrode arrangements depended on the nature of the task (i.e. “fine motor” vs “gross motor”) a two-way rmANOVA with factors of tDCS (anodal, cathodal, bihemispheric) and dexterity (“fine motor”, “gross motor”) was used with change expressed relative to sham by subtracting the value for the sham session (- sham).

2.6.3 *Transcallosal inhibition*

A one-way rmANOVA with factors of tDCS (sham, anodal, cathodal, bihemispheric) was used for the change in iSP duration for each hand separately, to determine whether the change in TCI depended on tDCS condition.

2.6.4 Relationships between variables

Pearson correlations were used to assess for relationships between change in iSP duration (ipsilesional to contralesional M1 TCI) and sequence specific learning (OT difference between last repeated and random block) or JTT change, expressed relative to sham. Due to multiple correlations an adjusted significance of $p < 0.01$ was used.

3. Results

One participant withdrew from the study due to a headache after the first experimental session (sham tDCS), leaving 24 for analysis. There were no other reported adverse effects. Participants commonly reported a transient itching sensation during tDCS or no sensation at all.

3.1 Corticospinal excitability

RMT was significantly higher for the ipsilesional M1 (median (range) 63.5 (32–100) % MSO) than the contralesional (52.5 (31–80) % MSO, Wilcoxon signed rank test $p = 0.002$). This indicates an overall imbalance in corticospinal excitability across the hemispheres, as expected.

3.2 Motor sequence learning task

The absolute OT of the first repetition did not differ across the sessions (Friedman test, $p = 0.950$), indicating consistency in baseline reaction times. The two-way rmANOVA revealed an effect of block ($F_{2,3,51.7} = 14.956$, $p < 0.001$) indicating that OT reduced with training, but

no effect of tDCS ($F_{3,69} = 0.839$, $p = 0.477$) and no interaction ($F_{10.6,244.0} = 0.932$, $p = 0.508$).

This indicates that improvements in OT with learning were unaffected by tDCS (Fig. 3A).

There was a significant increase in OT from the last block of the repeated sequence to the random block (effect of block: $F_{1,23} = 45.117$, $p < 0.001$) indicating that improvements in OT were specific to the trained sequence (Fig. 3A). There was no effect of tDCS ($F_{3,69} = 0.539$, $p = 0.657$) or interaction between block (last repeated, random) and tDCS ($F_{3,69} = 0.753$, $p = 0.524$). Similarly, there was no effect of tDCS on sequence specific learning (OT difference; $F_{3,69} = 0.774$, $p = 0.513$).

3.3 Speed-accuracy trade-off (PI)

The two-way rmANOVA with log-transformed data showed no effect of block ($F_{5,6,129.5} = 1.456$, $p = 0.202$) or tDCS ($F_{3,69} = 0.202$, $p = 0.894$) on the PI and no interaction ($F_{11.9,273.8} = 1.370$, $p = 0.181$). There was also no difference between the last repeated block and the random block (effect of block: $F_{1,23} = 0.351$, $p = 0.560$) and no interaction with tDCS ($F_{3,69} = 0.249$, $p = 0.862$). This indicates that there was no change in the speed-accuracy trade-off with training or with tDCS. Figure 3B shows non-transformed data for each tDCS condition.

3.4 Jebsen Taylor Test performance

Initial JTT time varied considerably across participants (see Table 1) indicating a range in upper limb function. The baseline (pre-stimulation) JTT did not differ across the sessions (Friedman test $p = 0.246$; Fig 4A). The one-way rmANOVA showed an effect of tDCS on the % Δ JTT time ($F_{3,69} = 5.194$, $p = 0.003$; Fig 4B). *Post-hoc* comparisons (one-tailed paired samples t-tests, with Bonferroni adjusted p value) showed that JTT time was significantly

reduced after anodal ($-7.7 \pm 2.0\%$, $p = 0.006$, effect size $d = 1.0$) and cathodal ($-8.2 \pm 2.5\%$, $p = 0.003$, $d = 0.7$) tDCS compared with sham ($0.7 \pm 1.4\%$), but not after bihemispheric ($-2.2 \pm 1.9\%$, $p = 0.371$, $d = 0.4$).

When divided into “fine motor” and “gross motor” subsections, expressed relative to sham, there was a tendency toward an effect of tDCS ($F_{2,46} = 3.108$, $p = 0.054$) as there tended to be a greater improvement with anodal or cathodal tDCS compared with bihemispheric. There was no difference between the subsections (effect of dexterity; $F_{1,23} = 2.090$, $p = 0.162$) or interaction between tDCS and dexterity ($F_{1,6,37.1} = 0.017$, $p = 0.967$) indicating that the improvements with active tDCS were independent of task type (Table 2).

3.4.1 JTT subgroup analyses

To explore further the effect of electrode arrangement on JTT performance, subgroup analyses were conducted with groupings based on time since stroke (< 6 vs > 6 months post-stroke), hand affected (dominant vs non-dominant) and stroke location (subcortical vs cortical), using % Δ JTT expressed relative to sham by subtraction (-sham), with age and initial JTT entered as potential co-variables. Average values for each subgroup are presented in Table 2.

There was no effect of time since stroke (< 6 months $n = 10$, > 6 months $n = 14$; $F_{1,20} = 1.211$, $p = 0.284$), and no interaction between tDCS and time since stroke ($F_{2,40} = 1.743$, $p = 0.188$). This suggests that the within-session improvements in JTT were independent of whether the stroke was recent (<6 months) or not.

There was a significant effect of hand ($F_{1,20} = 6.527$, $p = 0.019$), but no interaction with tDCS ($F_{2,40} = 0.656$, $p = 0.524$). This suggests that the group with their previously dominant hand affected ($n = 14$) had a greater improvement across all active conditions than the group with the non-dominant hand affected ($n = 10$).

There was a significant effect of location ($F_{1,20} = 16.032$, $p = 0.001$), but no interaction with tDCS ($F_{2,40} = 0.611$, $p = 0.548$). This suggests that the group with stroke affecting the cortical structures of the brain ($n = 8$) demonstrated greater improvement across all active conditions than the group with only subcortical structures affected ($n = 16$).

3.5 Transcallosal inhibition

The change in TCI was assessed from the ipsilesional to contralesional M1 (“unaffected” FDI) for 21 participants, and from the contralesional to ipsilesional M1 (affected FDI) for 11 participants as the remainder were unable to produce consistent EMG activity with their paretic hand.

To ensure that pre-stimulus voluntary activation (RMS EMG) was consistent pre-post stimulation and across sessions a two-way rmANOVA was used for each hand separately.

There was no effect of tDCS (sham, anodal, cathodal, bihemispheric), or time (pre, post) and no interaction for either hand (all p values > 0.1).

The one-way rmANOVA showed no effect of tDCS on the change in iSP duration from either hand (ipsilesional to contralesional M1 TCI: $F_{3,60} = 1.157$, $p = 0.334$; contralesional to

ipsilesional M1 TCI: $F_{3,30} = 0.352$, $p = 0.788$), indicating that there was no change in TCI as a result of tDCS (Table 3).

3.6 Relationships between variables

There were no significant correlations between the change in iSP duration (ipsilesional to contralesional M1 TCI) and sequence specific learning or change in JTT (- sham) for any active tDCS condition ($p > 0.07$, Table 4).

Since JTT was found to improve following unilateral tDCS, but not bihemispheric, Pearson correlations were also used to assess whether the response to each active stimulation condition correlated with the response to either of the other active conditions. The improvement with anodal tDCS correlated with cathodal ($R = 0.61$, $p = 0.002$), but neither unilateral condition correlated with bihemispheric (anodal with bihemispheric $R = 0.37$, $p = 0.075$, cathodal with bihemispheric $R = 0.13$, $p = 0.542$).

4. Discussion

This study demonstrated significant improvements in JTT performance following anodal or cathodal tDCS, but not following bihemispheric stimulation. It is the first study to demonstrate, in chronic stroke survivors, a clear effect of electrode arrangement on tasks that reflect activities of daily living. However, there was no effect of tDCS on the experimental motor sequence learning task or transcallosal inhibition from either hemisphere.

Although there have been numerous studies of the effects of tDCS in promoting motor function after stroke there is limited research regarding the effects on motor sequence learning with the paretic arm. This is likely due, at least in part, to a lack of experimental paradigms that can be performed with a paretic arm. The current study utilised a novel paradigm requiring gross arm movements and demonstrated significant improvements in movement preparation, i.e. reduction in OT, with learning of the sequence. However, tDCS of M1 was not found to alter learning, regardless of the electrode arrangement. Similarly, the speed-accuracy trade-off (PI) was unaffected. In contrast, two previous studies have demonstrated improvements in learning with active tDCS in comparison with sham (Lefebvre et al. , 2012b, Zimmerman et al. , 2012). It is possible that the paradigm utilised here may not have been sensitive enough to detect improvements with tDCS. The sequential tap task used by Zimmerman et al. (2012) required fine finger control, and the circuit task used by Lefebvre et al. (2012b) likely had a higher accuracy requirement than the current task, which may have left more room to demonstrate improvements. This suggests that not all movements are improved by tDCS. A recent systematic review indicates that, although some studies show improvements in motor learning with tDCS, there are overall no significant effects of tDCS across the different types of experimental motor learning tasks (Hashemirad et al. , 2016). One session of tDCS may therefore be insufficient to induce consistent changes in motor sequence learning. Repeated interactions between tDCS and motor learning are likely necessary to induce persistent changes.

Surprisingly there was no change in the speed-accuracy trade-off (PI) with training of the movement sequence. This suggests that although participants were able to anticipate target appearance and prepare their movements in advance, the quality of their movement did

not change with practice. This may be because, in this explicit learning task, participants were more focused on the time to leave the central square and anticipation of target appearance than they were on the speed and accuracy of their movements once the cursor left the central square. The result therefore may have been different if learning was “implicit” as the explicit learning paradigm could have narrowed their attention. Alternatively, improvements in movement quality with training may have been masked by fatigue as participants used their paretic arm.

Performance on the JTT improved significantly following anodal tDCS of ipsilesional M1 or cathodal tDCS of contralesional M1, but not after bihemispheric tDCS. Previous studies have also found improvements in JTT performance with active tDCS (Fregni et al. , 2005, Hummel et al. , 2005, Mahmoudi et al. , 2011), but those which have attempted to systematically compare JTT improvements across electrode arrangements have been limited by small sample sizes (Fregni et al. , 2005, Mahmoudi et al. , 2011) making it difficult for them to draw conclusions. It is therefore important that we have been able to confirm their findings of improvements following unilateral tDCS with a larger sample size. Additionally, to our knowledge this is the first study to demonstrate JTT improvements following unilateral tDCS in the absence of improvements with bihemispheric stimulation. Our results are consistent with those of O’Shea et al. (2014) who found improvements in a simple reaction time paradigm with anodal or cathodal tDCS only and extend their finding to more functional tasks that reflect activities of daily living. We found the response to anodal and cathodal tDCS to correlate with each other, suggesting that with mild and moderate levels of upper limb impairment it may not matter which cortex is targeted. However, this may not be the case for those with severe impairment (Bradnam et al. , 2012).

It was perhaps surprising that JTT performance improved *after* tDCS, given that learning, speed and accuracy were not changed *during* tDCS. The motor sequence learning task and the JTT were testing different aspects of motor performance. The JTT does not depend on sequence learning as participants are aware of the exact requirements of each task. Improvements are therefore gained by improving motor skill, through better control of muscle activation patterns. The results therefore suggest that only some movements are improved by tDCS. It is important to further understand this if tDCS is to be applied as an adjuvant to rehabilitation after stroke. Additionally, it is possible that the tDCS may have interacted with the motor practice (i.e. the controlled movement of the computer mouse) to reduce inhibition within the ipsilesional motor cortex and improve motor control, leading to improved JTT performance which persisted after completion of the stimulation. This is consistent with the findings of Hummel et al. (2005) that JTT improvements persisted for at least 25 minutes after anodal tDCS. Changes in cortical excitability and intracortical inhibition have also been shown to persist after the stimulation is turned off (Ardolino et al. , 2005, Stagg et al. , 2009, Di Lazzaro et al. , 2012, Bastani et al. , 2013b, a, Kidgell et al. , 2013, Kim et al. , 2014, Moliadze et al. , 2014).

The reason why bihemispheric tDCS was ineffective is unknown, but likely due to differences in the structures stimulated and the changes in connectivity between brain regions relative to the unilateral arrangements (Sehm et al. , 2012, Sehm et al. , 2013, Opitz et al. , 2015, Lindenberg et al. , 2016, Naros et al. , 2016). Modelling studies demonstrate that current spread is dependent on the distance between the two electrodes and is therefore likely to differ between unilateral and bihemispheric arrangements. Current density is greatest

below the anode for unilateral stimulation, spreading toward premotor and frontal areas which would also contribute to motor preparation. For the bihemispheric arrangement there is a medial shift of the current density (Opitz et al. , 2015, Naros et al. , 2016). Resting state fMRI also indicates different cortical network changes depending on the electrode arrangement (Sehm et al. , 2012, Sehm et al. , 2013, Lindenberg et al. , 2016), but the relationship between change in connectivity and motor function is not yet fully understood. Further research is required to gain more of an understanding about the differences in neural activity following bihemispheric vs unilateral tDCS and how these changes relate to improvements in motor function after stroke.

There was no change in TCI as a result of tDCS and no associations between the change in JTT and TCI from the ipsilesional to the contralesional M1 for any of the electrode arrangements. It therefore may be considered surprising that cathodal tDCS of the contralesional M1 was effective at improving JTT performance without changes in TCI from the contralesional M1. However, the iSP is just one method for assessing transcallosal inhibition. It is possible that differences would have been observed using the paired pulse (dual coil) technique, or that changes in interhemispheric connectivity could have been detected using fMRI. Unfortunately, it was not possible to utilise either of these methods for this study due to pragmatic considerations. Additionally, some of the patients were unable to produce consistent muscle activity with their affected hand, which limited the assessment of TCI from the contralesional to ipsilesional M1 to just 11 patients.

The hemisphere affected by the stroke influenced the response to tDCS, with greater JTT improvements for the group with the dominant hand affected. Similar findings were

reported with bihemispheric stimulation for a simple reaction time task (O'Shea et al. , 2014) and for the change in motor function after three weeks of repetitive TMS to the contralesional M1 (Ludemann-Podubecka et al. , 2015). The explanation for this hemispheric difference may lie in the susceptibility of M1 to adapt. Schade et al. (2012) demonstrated, in healthy adults, a larger increase in MEP amplitude with anodal tDCS when delivered to the dominant M1 compared with the non-dominant. We speculate that the dominant M1 may be more responsive to electrical stimulation, which could translate into greater functional changes. This finding therefore warrants further investigation. Additionally, the group with stroke involving the cortical structures demonstrated greater improvement with active tDCS than those with subcortical stroke. This is perhaps unexpected as subcortical stroke is thought to spare the grey matter regions that are predominantly stimulated by the tDCS. Some previous studies have shown greater improvement for those with subcortical stroke (Hesse et al. , 2011, Mahmoudi et al. , 2011), but others have suggested no difference in response (Lefebvre et al. , 2012b, O'Shea et al. , 2014). In the current study there were only eight participants with cortical involvement so the findings presented here should be interpreted with caution. Although initial JTT was entered as a covariate in the analysis, the possibility that differences between groups for neurophysiological characteristics (such as corticospinal tract excitability or resting inhibition) influenced this result cannot be discounted. A greater proportion of the cortical group (6/8) had their previously dominant hand affected, compared with the subcortical group (8/16). Given that we have reported a greater improvement in JTT with active tDCS for the group with the dominant hand affected, this could have influenced the result of this analysis. Therefore, larger studies to specifically address the issue of stroke location are required.

There are several limitations of this study to consider. The sample size, although greater than many studies of this nature, may have been insufficient for the subgroup analyses and therefore those findings should be interpreted cautiously. Although the motor sequence learning paradigm allowed people to participate who were more impaired than previous studies, it was still not possible to include people with the full range of impairment seen after stroke. The use of the within-subject crossover design allowed a systematic investigation, but also meant that the study could not be conducted in the early stage after stroke when rapid changes in cortical activity and function would have been occurring. It is therefore possible that the response would differ for people within the first three months of their stroke. There is currently limited research at the acute stage of stroke recovery, and studies are required to determine whether tDCS could be of benefit as part of routine clinical practice.

Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

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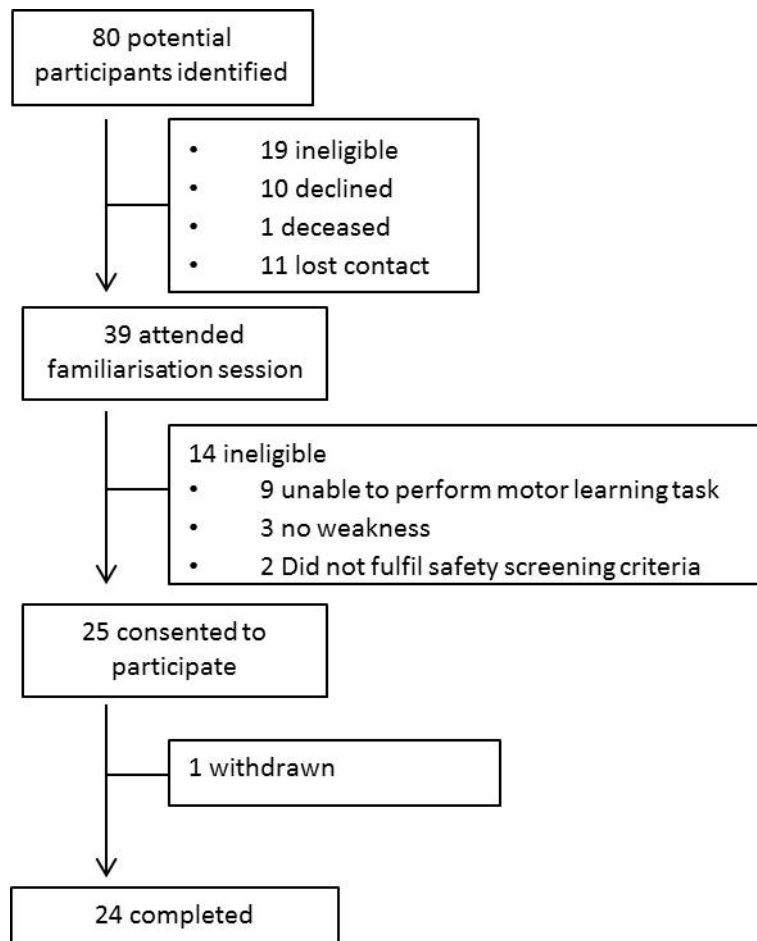
Figure Legends

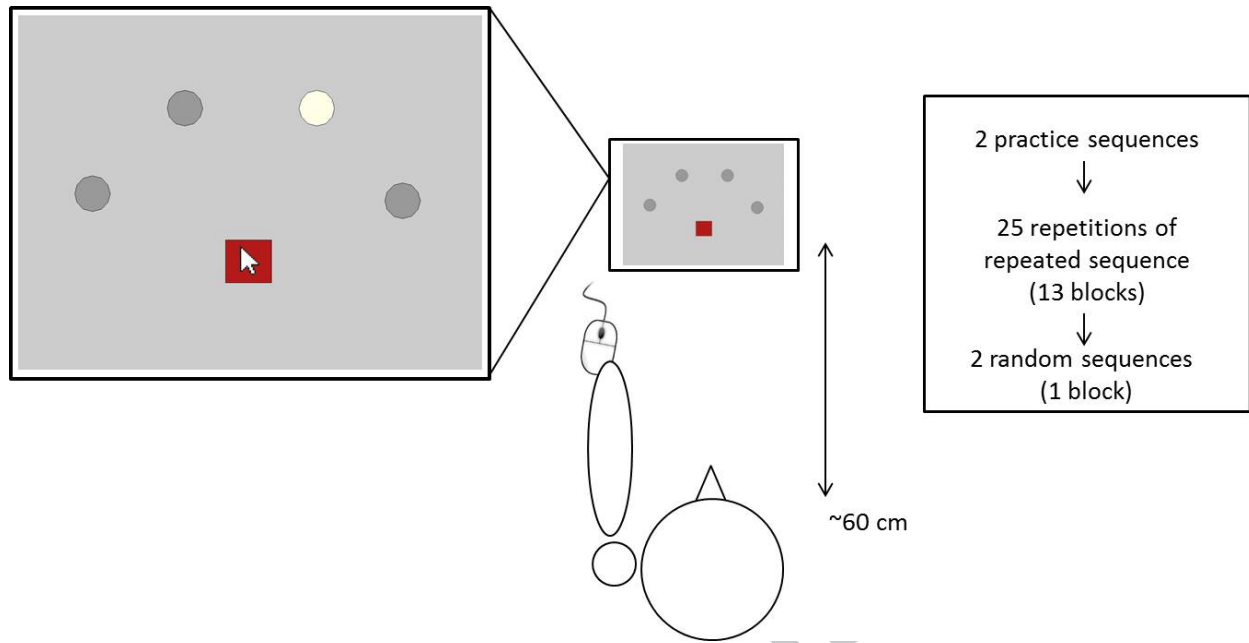
Fig. 1. Recruitment of participants.

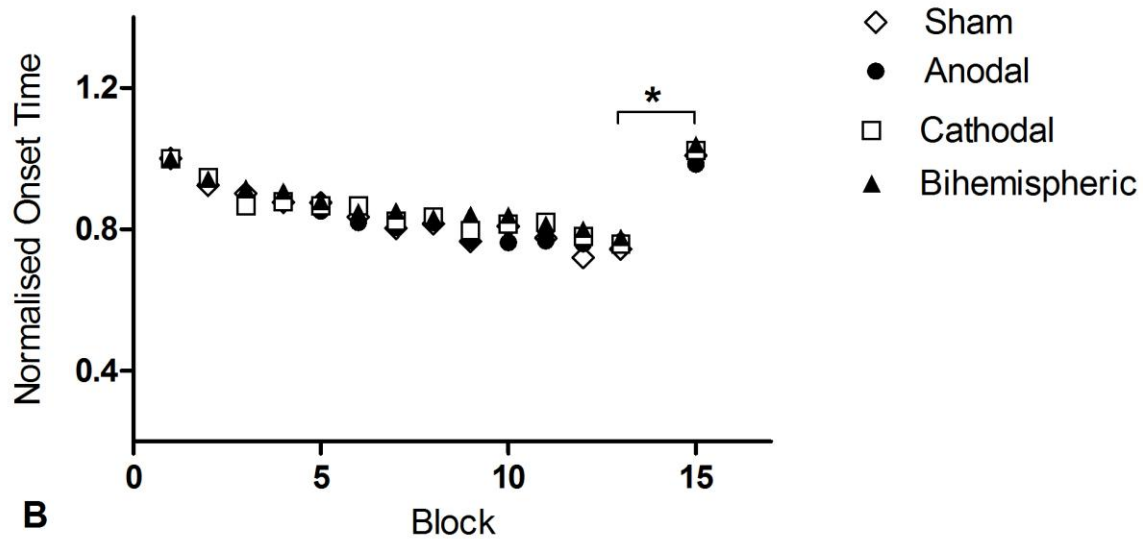
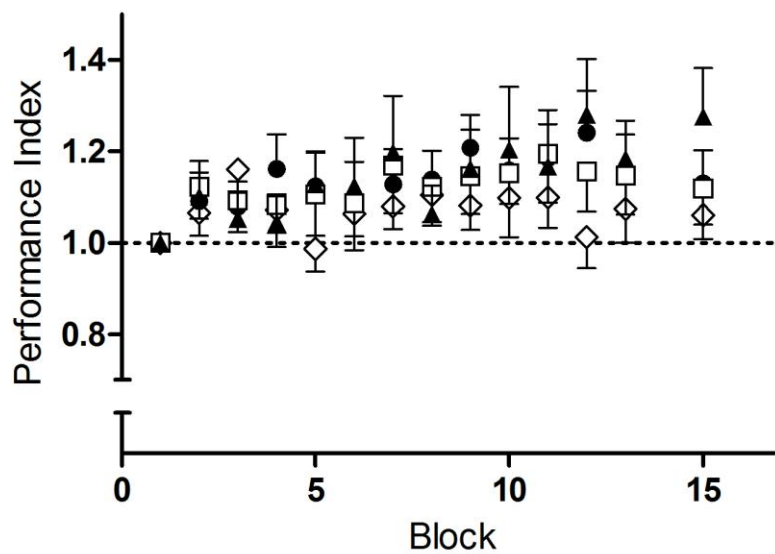
Fig. 2. Representation of experimental setup showing motor sequence learning programme as seen on the computer monitor. One central square and four circular targets can be seen. The circular targets were illuminated to form a 12 movement sequence. In each experimental session 13 blocks of the repeated sequence were performed, followed by a random block. Adapted from Fleming et al., 2016.

Fig. 3 A. Normalised OT and **B.** PI blocks. Block 15 represents the random sequence. There was a significant reduction in OT across the blocks. * significant difference between last repeated block and random block, $p < 0.05$.

Fig. 4A. Average JTT time pre- and post-stimulation for each tDCS condition. **B.** Percentage change in JTT time for each tDCS condition. Negative values indicate faster performance post-stimulation. * significant difference from sham, $p < 0.05$ with Bonferroni correction.





A**B**

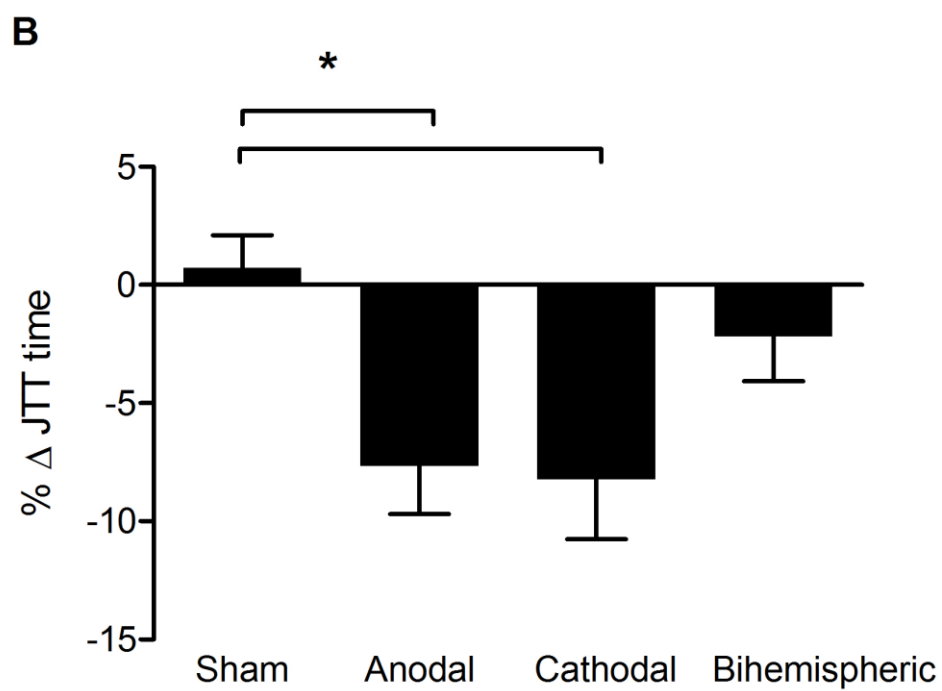
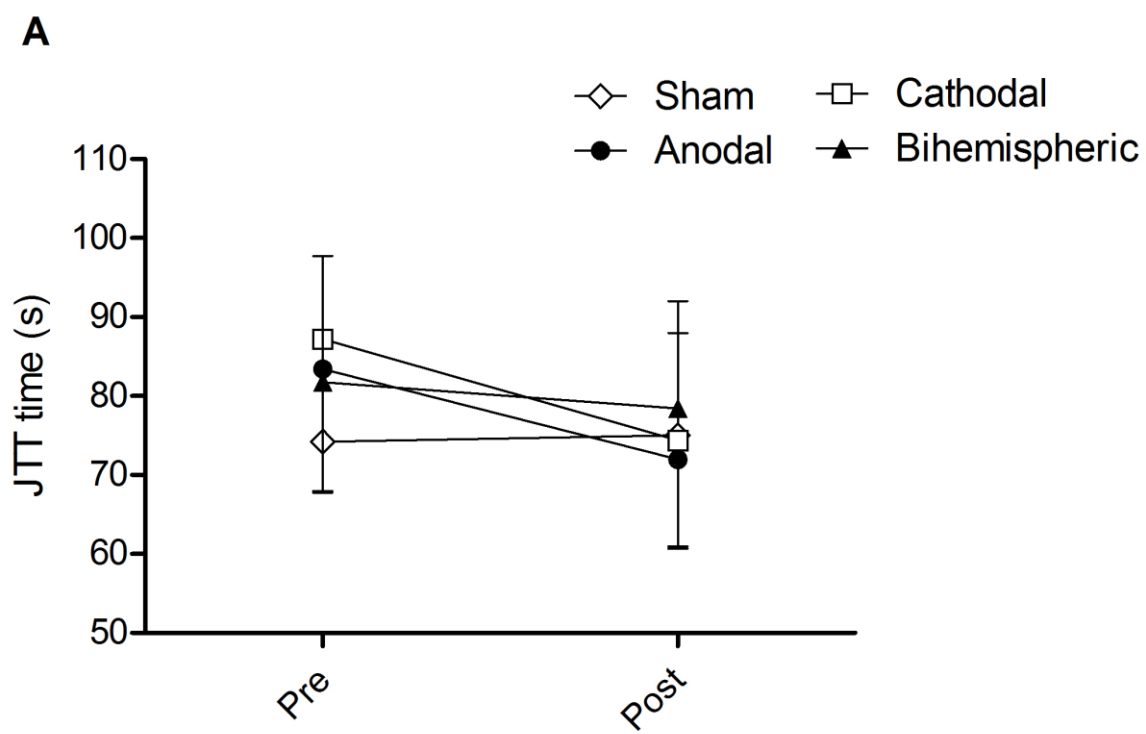


Table 1. Participant characteristics.

Participant	Age (years)	Time since stroke (months)	Affected hand	Dominant hand	Initial JTT (s)	Type of stroke	Location of stroke	MEP status (+/-)
1	52	46	R	R	77.5	H	C	+
2	67	124	R	R	46.0	I	S	+
3	62	32	R	R	44.7	I	S	+
4	57	43	R	R	45.3	I	S	-
5	76	10	L	L	29.7	I	C	-
6	39	13	L	R	94.1	I	S	+
7	65	3	L	L	65.6	I	C	+
8	39	54	L	R	131.2	H	S	+
9	59	6	L	R	52.25	I	C/S	-
10	66	52	R	R	281.3	I	C	
11	34	26	R	R	314.11	I	S	-
12 ^a	81	4	R	R	43.07	I	S	+
13	63	6	L	R	44.16	I	S	+
14	63	5	L	R	33.09	H	S	+
15	61	9	R	R	36.19	I	C	+
16	62	7	L	R	30.06	I	C	+
17	36	3	R	R	61.94	H	S	-
18	67	4	R	R	99.06	I	C	+
19	56	7	L	R	54.01	I	S	+
20	69	3	R	R	40.26	I	S	+
21	74	3	L	R	43.95	I	S	+
22	50	7	L	R	132.27	I	S	-
23	76	20	R	R	52.38	I	S	-
24	47	3	R	R	34.67	I	S	+
25	74	3	L	R	47.59	I	S	+
Min	34	3			29.7			
Max	81	124			314.1			
Mean	59.8	19.7			77.4			
(SD)	(13.1)	(27.4)			(72.2)			
Median	62	7			47.6			
Number			13 R/ 12 L	23 R/ 2 L		4 H / 21 I	8 C / 16 S	17+/7-

^a withdrawn before completion. JTT=Jebsen Taylor test time, R=right, L=left, I = Ischaemic, H = Haemorrhagic, S = subcortical, C = cortical, SD=standard deviation. MEP status refers to the presence (+) or absence (-) of motor evoked potentials in response to transcranial magnetic stimulation (note. TMS was not performed for subject 10).

Table 2. Subgroup analyses JTT % change relative to sham (mean \pm SEM).

	Anodal	Cathodal	Bihemispheric
Dexterity			
Fine motor	-9.6 \pm 3.3	-10.4 \pm 3.3	-4.3 \pm 3.2
Gross motor	-5.1 \pm 2.6	-6.3 \pm 2.5	-0.47 \pm 3.1
Time since stroke			
< 6 mo, n = 10	-9.0 \pm 2.8	-5.6 \pm 3.0	-6.3 \pm 3.0
> 6 mo, n = 14	-7.9 \pm 3.9	-11.4 \pm 3.6	-0.5 \pm 3.4
Hand affected*			
Dominant, n = 14	-11.4 \pm 3.9	-14.4 \pm 3.2	-6.0 \pm 3.3
Non-dominant, n = 10	-4.1 \pm 2.2	-1.3 \pm 2.6	1.4 \pm 2.9
Stroke location*			
Cortical, n = 14	-18.7 \pm 4.5	-17.0 \pm 5.1	-7.6 \pm 5.1
Subcortical, n = 16	-3.2 \pm 2.1	-5.0 \pm 2.2	-0.6 \pm 2.3

*significant effect of group, $p < 0.05$. mo = months

Table 3. Baseline and within session change in iSP duration.

	Ipsilesional to contralesional M1 TCI (unaffected FDI, n = 21)				Contralesional to ipsilesional M1 TCI (affected FDI, n = 11)			
	S	A	C	B	S	A	C	B
Baseline (ms)								
Mean	23.4	24.0	26.4	25.6	44.0	40.9	41.6	40.1
(SEM)	(2.4)	(2.4)	(2.7)	(3.0)	(6.5)	(5.6)	(5.8)	(6.0)
Change (ms)								
Mean	2.6	1.7	-0.3	0.5	-1.8	1.0	-0.6	1.6
(SEM)	(1.6)	(1.0)	(1.0)	(0.9)	(2.9)	(2.2)	(3.4)	(2.6)

S = sham, A = anodal, C = cathodal, B = bihemispheric. FDI = first dorsal interosseus.

Table 4. Pearson correlations between change in TCI (iSP duration) from ipsilesional to contralesional M1 and sequence specific learning (OT difference between last repeated block and random block) and JTT change relative to sham.

	OT difference		JTT	
	R	p	R	p
Anodal	-0.392	0.079	0.235	0.305
Cathodal	-0.042	0.857	0.089	0.700
Bihemispheric	0.188	0.414	-0.008	0.973